interpreted, in its broadest sense, to encompass an entire naturally occurring genomic DNA molecule or chromosome."

Applicants respectfully traverse the Examiner's rejection. Claim 47 recites a "recombinant DNA" comprising a "fragment of genomic DNA." Applicants respectfully submit that the claimed "fragment" by definition alone would not encompass an entire chromosome. Additionally, the claim requires that the DNA be a "recombinant DNA," which should be appreciated by the Examiner as indicating the work of man in its construction, and as such said DNA is not "a product of nature."

Applicants believe that the rejection of claim 56 under section 101 is rendered moot by the present amendment to that claim.

Relying on 35 U.S.C. §112, first paragraph, the Examiner has rejected claims 53 and 54, alleging that there is insufficient detail in the specification to enable one of ordinary skill in the art to "exactly duplicate" the plasmids, and requiring deposit of the claimed plasmids. Applicants request that the Examiner hold his requirement for deposit in abeyance until such time as the claims are deemed otherwise allowable.

The Examiner also has rejected claims 39 and 40, alleging that the disclosure is enabling only for the hamster GS gene, and recites a scheme he believes is necessary in order to isolate a different GS gene. Applicants respectfully disagree with the Examiner's characterization of the required experimentation. Applicants submit that at the time of their invention the skilled

worker would need only perform routine experimentation in order to isolate other mammalian or rodent GS genes. Applicants refer to the Alberts et al. and Watson et al. publications cited by the Examiner as to the level of the routine nature of the experimentation required.

The Examiner has also rejected claims 57 and 59 as non-enabled. Applicants respectfully disagree with the Examiner. Applicants have an enabling disclosure for a myeloma cell as well as a mammalian myeloma cell as recited in the claims. Applicants again respectfully refer to the level of skill in the art.

With reliance on 35 U.S.C. §112, second paragraph, the Examiner has rejected claims 44 and 56 to 59 as indefinite. With respect to claim 44, the Examiner specifically objects to the terminology "high stringency conditions." Applicants respectfully submit that the terminology objected to is well known to those of skill in the art is described in undoubtedly countless research articles. The Examiner also objects to "a part thereof from a different species" in claim 44. Applicants submit that the claim language is definite in that it clearly refers to either the full sequence of a GS gene from a different species or a part, for example a restriction fragment, of that GS gene. The Examiner further objects to the language of claim 44, stating that it is unclear what "mammalian species" applicants are referring to. Applicants submit that this wording is clear in that they are referring to any mammalian species.

With respect to the section 112, second paragraph rejection of claims 56 to 19, Applicants believe that their amendment to claim 56 renders this rejection moot.

The Examiner has also rejected claims 39 to 47, 50, 51 and 55 under 35 U.S.C. §103 over Sanders et al. in view of Alberts et al. or Watson et al.. Applicants traverse the Examiner's rejection.

The Examiner has characterized the present invention as "the logical conclusion of the work of Sanders et al.." Applicants respectfully disagree with such a characterization of their invention. Sanders et al. is an academic paper relating to an investigation of the GS gene in CHO cells. Sanders et al. show that the genomic GS gene can be amplified by exposing CHO cells to increasing levels of Msx. Sanders et al. also purportedly reports the partial cloning of the GS gene (see below). However, Sanders et al. do not show the cloning of the complete GS gene, nor does it in any way relate to the use of the GS gene as a selectable marker or in co-amplification processes.

In particular, Applicants respectfully submit that the Sanders et al. paper points away from the use of a GS gene in the above processes. The fact that the endogenous gene in CHO cells can be amplified in its natural chromosomal environment would lead a skilled artisan to expect that the amplification of the endogenous gene would prevent selection of transformants containing amplified exogenous GS genes. Applicants simply fail to see how a skilled

artisan could gain any incentive from Sanders et al. even to consider using a GS gene as a tool in recombinant DNA technology, let alone in the specific methods now claimed.

In this regard, Applicants note that Examiner states that the motivation for combining the cited references is the "potential use in coamplifying an additional foreign gene of interest." Applicants can find this motivation in none of the cited references. Rather, Applicants respectfully submit that this alleged motivation for this "potential" is first disclosed in their specification. Applicants respectfully submit that such use of their disclosure in formulating a rejection is improper hindsight on the part of the Examiner.

The Examiner has also cited the fact that Applicants used the procedure of Sanders et al. to generate their GS clone in support of his rejection of the claims. Applicants respectfully submit that reference to their disclosure in order to justify a conclusion that is not supported by the cited publication is again an example of improper hindsight.

In addition to the above, Sanders et al. report isolation of a large DNA fragment which may or may not have actually encoded part of the GS protein. The publication presents no nucleotide sequence information on the pGS1 clone through which the ordinary artisan could conclude that the GS genomic DNA had in fact been isolated.

The cloning of the GS gene was not established in fact until the present invention, when the cDNA for GS was isolated, fully sequenced and this sequence compared to the DNA sequence of bovine brain GS and Anabaena GS. Also establishing that GS was in fact cloned and complete in the present invention are the biochemical studies disclosed in the specification wherein resistance to methionine sulphoximine was conferred on Msx sensitive cells by the expression of the cloned sequence in those cells.

In sum, Applicants respectfully submit that the Sanders et al. paper does not contain sufficient disclosure to lead the ordinary artisan to conclude that a complete GS gene had in fact been cloned. Even if the paper did contain this disclosure,

The Alberts et al. and Watson et al. are merely general disclosures with no apparent reference whatsoever to a complete GS DNA.

In light of the above, Applicants respectfully request that the Examiner's rejection of the claims over Sanders et al. in view of Alberts et al. or Watson et al. be withdrawn.

Relying on 35 U.S.C. §103, the Examiner has also rejected claims 52 to 54 and 56 to 60 over Sanders et al. in view of Alberts et al. or Watson et al. all further in view of Axel et al.. The Examiner cites Axel et al. for disclosing co-amplification. Applicants respectfully traverse the Examiner's rejection.

Applicants arguments concerning Sanders et al., Alberts et al. and Watson et al. are set forth above and incorporated in Applicants' response to the present rejection.

The Examiner has cited especially column 3 of the Axel patent. Applicants respectfully direct the Examiner's attention to column 3, lines 20 to 27, wherein it is stated:

> "This invention provides a process for inserting foreign DNA into eucaryotic cells by cotransforming the cells with this foreign DNA and with unlinked DNA which codes for proteinaceous material associated with **a selectable phenotype not otherwise expressed by the cell**. (emphasis added)

First, as to all the rejected claims, the Axel et al. patent is apparently directed solely to a selectable marker **that is not normally associated with or expressed in the transformed cell**. Axel et al. disclose only selectable markers of foreign origin. The Axel et al. patent does not disclose or suggest using a gene which is normally active in the recipient cell.

Thus, in great contrast to Axel et al., the glutamine synthetase selectable marker is a protein which is normally expressed in the transformed cells. Applicants respectfully submit that this alone makes their invention both novel and non-obvious in view of the references, and therefore respectfully request the Examiner withdraw this rejection of the claims.

Second, as to claims 56 to 60, none of the cited references disclose or suggest the use of glutamine synthetase to amplify a gene encoding a desired polypeptide or protein linked to a GS gene. Applicants fail to see where the cited publications disclose or suggest use of myeloma cells as specifically recited in claims 57

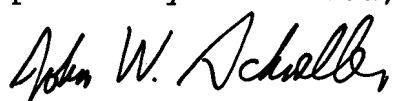
and 59, or of the CHO-KI myeloma cells as specifically recited in claim 58. Applicants therefore also respectfully submit that their invention as presently claimed is both novel and non-obvious for these additional reasons.

In light of the above amendments and remarks, Applicants respectfully request the Examiner to reconsider and withdraw each his rejections of the claims.

Applicants respectfully submit that their application is now in condition for allowance and request such notice in the next communication from the Examiner.

The Examiner is invited to call the undersigned attorney should any minor matter remain.

Respectfully submitted,



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